Excitable Cells: Active Properties

Introduction

In lesson #6: *Excitable Cells: Passive Properties*, we ended by defining "threshold stimulus." "Threshold" is the membrane potential at which special channels that are sensitive to voltage changes open. Until the threshold potential is reached, every one of these channels fails to open. When the threshold is crossed, all of these channels open with only a small delay. The opening of all of these special channels initiates the consistent, reproducible, and predictable **all-or-nothing** electrical tracing called the **action potential.** It is the activity (opening and closing) and to which ion the channel is permeable (Na^+ or K^+) that determine what the action potential will look like.

When the membrane becomes permeable to a particular ion, the established concentration gradient for that ion (the chemical force) allows ions of that kind to move down their concentration gradient. As more of that ion moves down the concentration gradient, the cell membrane voltage changes to balance that gradient by moving towards that ion's Nernst potential.

The more channels that are open to that ion determine how quickly those ions can flow and how quickly the membrane voltage changes to that ion's Nernst potential. If two channels are open, each to a different ion, then both ions will flow down their concentration gradient. The one that "wins" is the one with the highest membrane conductance—whoever has the most channels open.

Consider an example of Na^+ and K^+. The Nernst for Na^+ is +65, and it has a chemical force that drives it into the cell. The Nernst for K^+ is −95, and it has a chemical force that drives it out of the cell. If the membrane becomes permeable to Na^+, Na^+ rushes down its concentration gradient (into the cell), and the membrane voltage goes briskly towards the Nernst potential for Na^+. If the membrane becomes very permeable to K^+, K^+ rushes down its concentration gradient (out of the cell), and the membrane voltage goes briskly towards the Nernst potential for K^+. If the membrane conductance were equal for both, the membrane voltage would be the average of the two. But, as soon as the membrane conductance of one exceeds the other, the membrane voltage will tend towards the "winner." How fast it gets there reflects the actual difference in the membrane conductance of the ions.

A skeletal muscle action potential starts with a burst of Na^+ membrane conductance, then a sudden cessation of Na^+ membrane conductance. Along side this rapid open/rapid close of Na^+ channels there is a slower opening of K^+ channels.

Action Potential

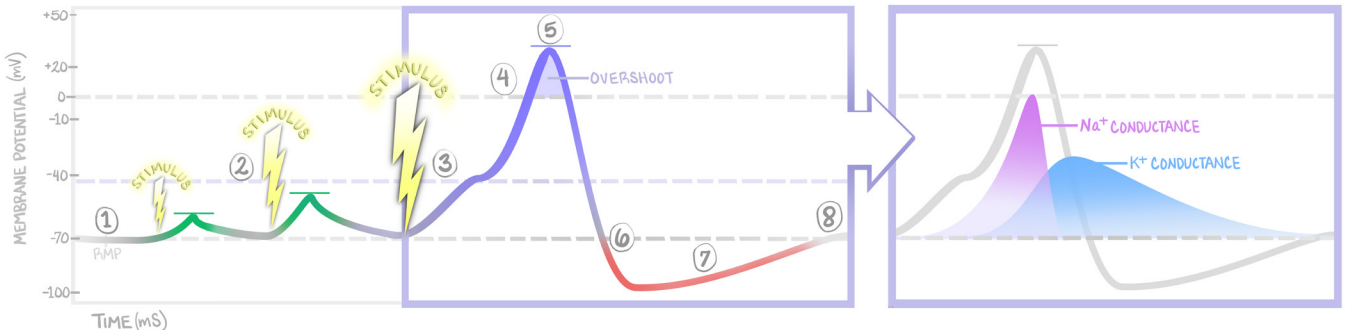

Figure 7.1: The Action Potential
Every time the threshold potential is reached, an identical sequence of events occurs, generating an action potential. Use this figure to follow along with the text.

1. Resting membrane potential is the voltage maintained across the cell membrane when it is at rest, without any stimuli.

2. Any stimulus delivered will depolarize the cell. This is a subthreshold stimulus, as it does not cause the cell to reach the threshold potential and instead causes a graded response.

3. When a threshold stimulus is delivered, threshold is reached, and a mass of **voltage-gated sodium channels opens**. This greatly increases the membrane conductance to sodium. Voltage-gated potassium channels have also reached their threshold, but are slower to open. There is nothing to oppose the sodium conductance.

4. Voltage-gated sodium channels are rapid to open and also rapid to close, dropping the membrane's conductance of Na^+ to zero. This is called **inactivation.** As the Na^+ channels are inactivating, **voltage-gated potassium channels** are opening. Conductance to K^+ increases.

5. At the peak, conductance of potassium overtakes conductance of Na^+. All Na^+ channels have inactivated. More K^+ open. Any depolarization above zero is called **overshoot**.

6. With only K^+ channels open, rapid **hyperpolarization** occurs. There is no Na^+ conductance to oppose K^+ conductance, so the cell goes below the resting potential all the way to the Nernst of K^+. These K^+ channels close only with hyperpolarization.

7. Hyperpolarization closes the K^+ channels. It also returns the Na^+ channels to their resting positions—neither open nor inactivated. No Na^+ flows. Some K^+ flows because as they were slow to turn on, these channels are slow to turn off. As they turn off, the cell tends towards the resting potential.

8. All voltage-gated channels are in their resting position, restoring the membrane potential to be dependent only on the leak K^+ channels and the Na^+/K^+-ATPase. This restores the electrochemical gradient to the resting potential. The cell is at rest.

Channels

Voltage-gated Na^+ channels have a gate on each side of the membrane. The activation gate faces the ECM and is described as either "open" or "closed." The inactivation gate is on the cytoplasmic side and is described as either "active" or "inactive." The channel has three states, based on conformation of these two gates: closed-active (resting state), open-active (allowing for ions to move through) and open-inactive (preventing ions from moving through).

The **activation gate** is **closed at rest**. Opening of the activation gate greatly increases conductance to sodium. The activation gate is **opened by threshold voltage** and is **closed by both threshold voltage and time**. That is, as the membrane potential moves from resting to threshold (about –60 mV for these channels), the activation gate opens. The gate will not reset to the closed resting position until the threshold is crossed again and sufficient hyperpolarization is achieved—from a voltage above threshold to a voltage below threshold. In addition to hyperpolarization, an amount of time must pass before the gate will close. It is not instantaneous.

The **inactivation gate** is **open at rest**, and closing the inactivation gate decreases conductance to sodium. The inactivation gate is **closed by threshold voltage** (only takes slightly longer to close than the activation gate takes to open) and is **opened by both threshold voltage and time**. The inactivation gate, like the activation gate, returns to its resting position only with hyperpolarization and time.

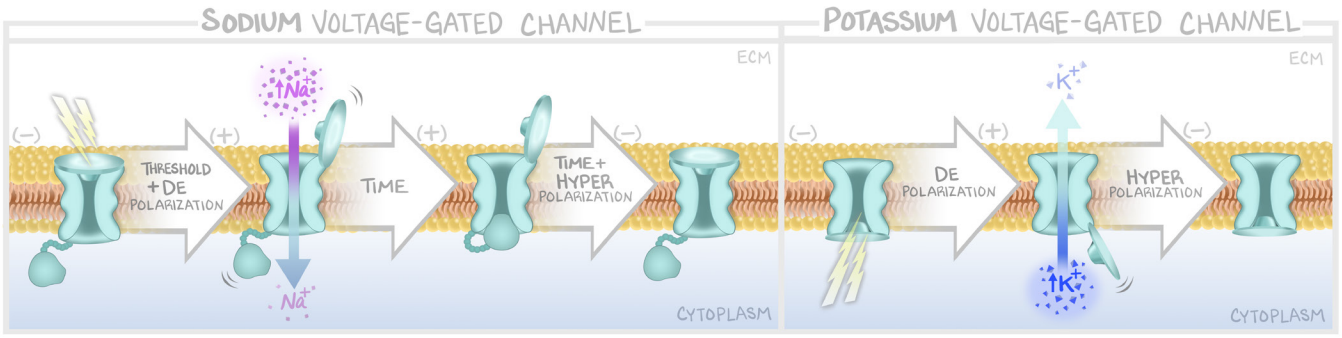

Figure 7.2: Voltage-Gated Channels
Voltage-gated sodium channels have both an activation gate (closed at rest, opened by depolarization) and an inactivation gate (open at rest, closed with depolarization), such that when threshold is reached, the conductance to sodium is increased massively, but only very briefly. The inactivation gate will remain closed until there is a hyperpolarizing stimulus to reset the gate. Voltage-gated potassium channels have an activation gate only, such that if the system were to activate (threshold was reached), the sodium channels would inactivate, and the potassium channels would remain open—the default state is to reset the system.

Voltage-gated K^+ channels also open by **depolarization** across threshold and close by **hyperpolarization** across threshold and time. These channels are **slower to open**, but also **slower to close**. Unlike voltage-gated sodium channels, they have no inactivation gate. This setup ensures that an excitable cell will depolarize when reaching threshold, but if something goes wrong, the sustained signal is K^+ (Na^+ inactivates, K^+ doesn't), hyperpolarizing the cell, silencing further action potentials.

Refractory Period

Because action potentials are dependent on reaching threshold, which is induced by Na^+ conductance, there's a phenomenon called a **refractory period**. The **absolute refractory period** is the time between crossing threshold on depolarization and crossing threshold on hyperpolarization. All voltage-gated Na^+ channels that open (activation gate opens) will all also inactivate (inactivation gate closes). The inactivation gate remains closed, the channel unable to open again until repolarization across threshold occurs. This is the time when a second action potential is impossible regardless of how much stimulus is applied. Adding more depolarizing stimulus to a closed-inactive channel will only result in keeping it in the closed-inactive state.

Opening of the inactivation gate and closure of the activation gate (resetting to the resting configuration) require **hyperpolarization and time.** Both are necessary because voltage-gated Na^+ channels don't all open at the same time, inactivate at the same time, or reset at the same time. As the last-to-open channels remain closed-inactive (soon to recover), other channels have already opened and closed, returning to the closed-active state. Over time, all the channels will recover to closed-active.

The initial threshold stimulus was reached due to the number of channels available to open. While some are still closed, that same magnitude of stimulus would not induce an action potential. However, a stimulus of larger magnitude could result in an action potential, even with fewer open channels available. This is known as the **relative refractory period**.

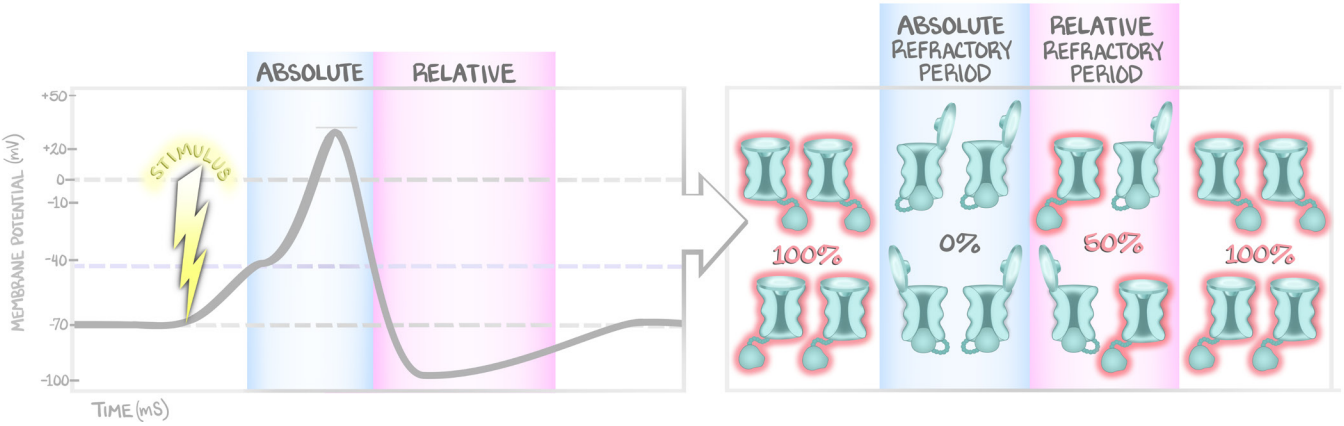

Figure 7.3: Absolute and Relative Refractory Period
There is a time (before hyperpolarization) when the sodium inactivation gates have not reset. No matter the stimulus, the inactivation gates are not open. This is the absolute refractory period. In the relative refractory period, some inactivation gates have recovered and some are still recovering, such that if a larger stimulus were applied, the population of closed-ready channels could invoke an action potential. Because there are fewer channels ready in the activation-closed/inactivation-open position, a more vigorous stimulus is required to initiate another action potential from baseline.

Propagation of the Action Potential: Cable Theory

As the threshold potential is reached locally, voltage-gated sodium channels open, inducing a massive depolarization. Those voltage-gated sodium channels that are nearby that did not reach the threshold potential based on the initial stimulus (so are still ready to open) now feel the massive depolarization of the action potential. They, too, open. Farther out from the initial stimulus are other voltage-gated sodium channels that did not reach their threshold yet. But as the second region depolarizes, it brings the third region to threshold. Each successive region of tissue close to a massive influx undergoes the same phenomenon, which propagates the action potential down the membrane.

But transmitting the signal from one place to another (e.g., finger to brain) requires that signal be carried over vast distance. This is analogous to transmitting an electrical impulse across a transatlantic cable. As the signal moves across the cable, signal is lost to the environment. All electrical signals degrade regardless of how well the cable is made. Signal loss and degradation always occur, due to resistance (heat), travel time, and distance.

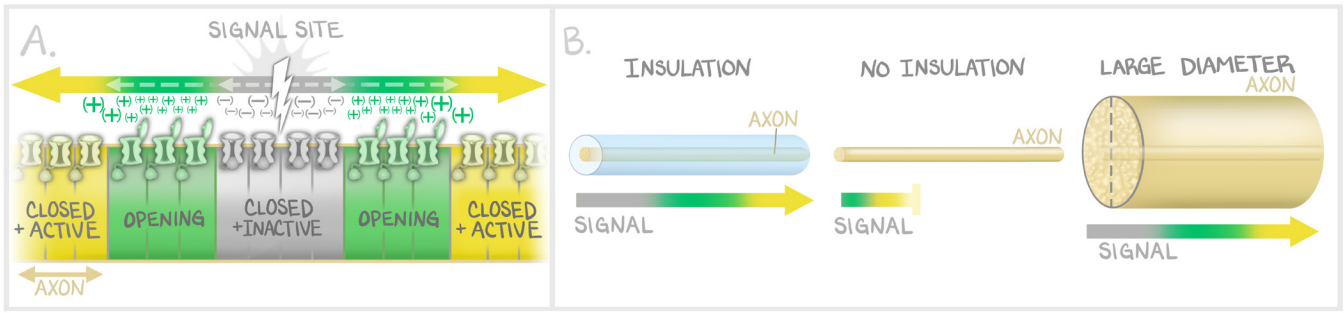

Figure 7.4: Action Potential Transmission
(a) Signal propagation can occur only from the source of the action potential away from that source, because only closed-active channels can open, while open-active channels are generating the action potential (and will soon inactivate) and closed-inactive have not yet recovered to the closed-active state. The refractory period prevents the signal from going backwards. (b) Axons ensure that the signal starts at one end and travels towards the other, as along a cable. Signal along a cable is lost; the electrical signal decays and is lost through the circumference of the cable. To maintain that signal, the cable can be made very thick (necessitating an enormous organism such as the giant squid) or insulated.

A signal can be sustained in two ways: limiting its degradation within the cable and/or amplifying it by a repeater. Human neurons use both.

Signal degradation can be limited by increasing the thickness of the cable (**large radius**) or by surrounding it with a protective material (**insulation**). Without insulation, the size of the axon must be enormous in order to prevent degradation of the signal. Giant squids and dinosaurs were huge, and likely didn't have insulation—they didn't need it because they instead went with large-radius axons ("cables"). Humans use insulation around their axons, allowing them to be super-thin, packing many into our spinal column, allowing us to be small. In the central nervous system this insulation is called **myelin**; in the peripheral nerves it's **Schwann cells**.

But since there's no such thing as perfect insulation, some signal is going to be lost, which is why human neurons also have a repeater system that enhances the signal. The **nodes of Ranvier** are breaks in the myelin sheath with a high density of sodium channels. As the action potential reaches the nodes, all the voltage-gated sodium channels open, resulting in massive depolarization. Tissue behind the signal becomes refractory, so the signal can only move in one direction—forward—to tissue that is not yet depolarized.

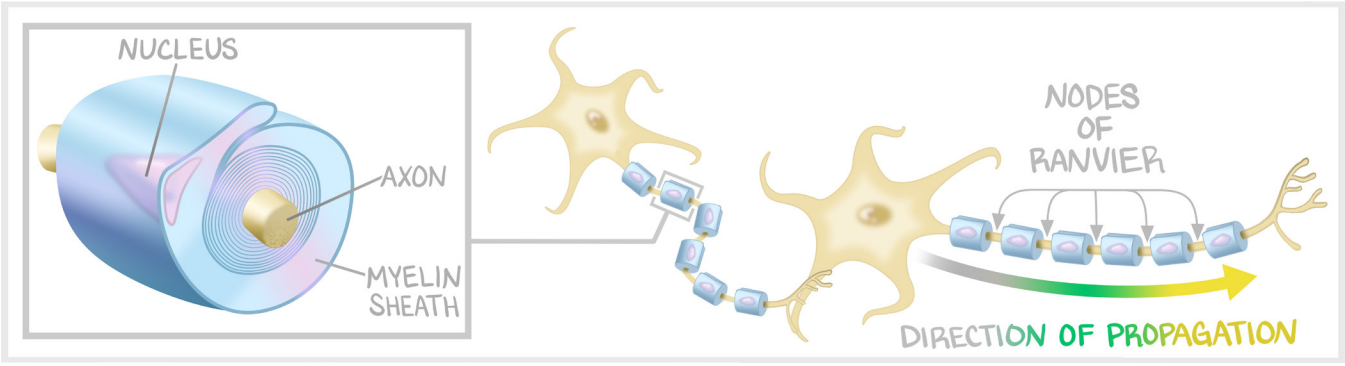

Figure 7.5: Limiting Signal Degradation
Nerves have two methods to minimize signal degradation. The entire cell is covered in a myelin sheath, functioning as insulation. The axon also has the nodes of Ranvier, areas dense with sodium channels which help to propagate the signal in the direction of tissue that has not yet been depolarized.

The areas insulated with myelin between the nodes have no Na^+ channels—this means there is no conductance. Because of this and because some signal will still be lost despite insulation, the nodes are vital to "re-up" the signal. Otherwise, the signal would quickly die out. This is a redundant fail-safe to keep the system propagating unidirectionally—if one node fails to reach threshold, two other nodes can induce action potential propagation, and recover the signal.